

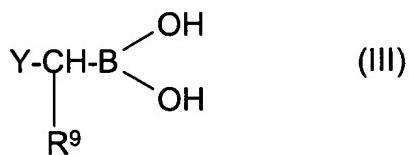
In the Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

Claim 1 (original): A salt of a pharmaceutically acceptable multivalent metal and an organoboronic acid inhibitor of thrombin having a neutral thrombin S1-binding moiety linked to a hydrophobic thrombin S2/S3-binding moiety.

Claim 2 (original): A salt of claim 1 wherein the organoboronic acid is of Formula (III):



wherein

Y comprises a moiety which, together with the fragment $-\text{CH}(\text{R}^9)-\text{B}(\text{OH})_2$, has affinity for the substrate binding site of thrombin; and

R^9 is a straight chain alkyl group interrupted by one or more ether linkages and in which the total number of oxygen and carbon atoms is from 3 to 6, or is $-(\text{CH}_2)_m-\text{W}$ where m is from 2 to 5 and W is $-\text{OH}$ or halogen (F, Cl, Br or I).

Claim 3 (original): A salt of claim 2 wherein R^9 is an alkoxyalkyl group.

Claim 4 (original): A salt of claim 2 wherein Y comprises an amino acid which binds to the S2 subsite of thrombin and is linked to $-\text{CH}(\text{R}^9)-\text{B}(\text{OH})_2$ by a peptide linkage, the amino acid being N-terminally linked to a moiety which binds the S3 subsite of thrombin.

Claim 5 (original): A salt of claim 4 wherein Y comprises an N-terminally protected dipeptide residue which binds to the S3 and S2 binding sites of thrombin and is linked to – CH(R⁹)-B(OH)₂ by a peptide linkage.

Claim 6 (original): The salt of claim 1 wherein the boronic acid has a Ki for thrombin of about 100 nM or less.

Claim 7 (original): The salt of claim 5 wherein the Y dipeptide is N-terminally protected or N-terminally unprotected, and the peptide linkages in the dipeptide are unsubstituted or independently N-substituted by a C₁-C₁₃ hydrocarbyl, wherein the C₁-C₁₃ hydrocarbyl contains no heteratoms or at least one in-chain or in-ring nitrogen, oxygen or sulfur atom, and the C₁-C₁₃ hydrocarbyl is unsubstituted or substituted by a substituent selected from halo, hydroxy and trifluoromethyl.

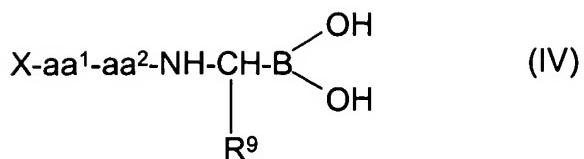
Claim 8 (original): The salt of claim 1 wherein the multivalent metal comprises calcium, magnesium or zinc.

Claim 9 (original): The salt of claim 1 wherein the salt consists essentially of an acid salt in which one B-OH group of formula (I), when trigonally represented, remains protonated.

Claim 10 (original): The salt of claim 7 wherein the salt comprises boronate ions derived from the peptide boronic acid and has a stoichiometry consistent with the boronate ions carrying a single negative charge.

Claim 11 (original): The salt of claim 3 wherein the salt consists essentially of a hemicalcium or hemimagnesium of the boronic acid.

Claim 12 (currently amended): ~~A salt of a pharmaceutically acceptable multivalent metal and The salt of claim 1 wherein [[a]] the peptide boronic acid is of formula (IV):~~



where:

X is H or an amino-protecting group;

aa¹ is an amino acid having a hydrocarbyl side chain containing no more than 20 carbon atoms and comprising at least one cyclic group having up to 13 carbon atoms;

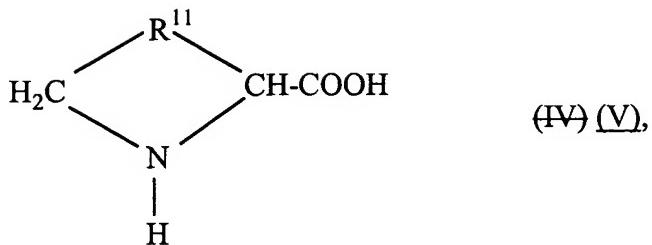
aa² is an imino acid having from 4 to 6 ring members;

R⁹ is a straight chain alkyl group interrupted by one or more ether linkages and in which the total number of oxygen and carbon atoms is from 3 to 6, or is -(CH₂)_m-W where m is from 2 to 5 and W is -OH or halogen R¹ is a group of the formula (CH₂)_s-Z, where s is 2, 3 or 4 and Z is OH, OMe, OEt or halogen.

Claim 13 (original): The salt of claim 12 wherein aa¹ is selected from Phe, Dpa and wholly or partially hydrogenated analogues thereof.

Claim 14 (original): The salt of claim 13 wherein aa¹ is of R-configuration.

Claim 15 (currently amended): The salt of claim 12 wherein aa² is a residue of an imino acid of formula (IV) (V)



where R^{11} is $-CH_2-$, $-CH_2-CH_2-$, $-S-CH_2-$, $-S-C(CH_3)_2-$ or $-CH_2-CH_2-CH_2-$, and, when the formula (IV) ring is 5- or 6- membered, the formula (IV) ring is unsubstituted or is substituted at one or more $-CH_2-$ groups by from 1 to 3 C_1-C_3 alkyl groups.

Claim 16 (original): The salt of claim 15 wherein aa^2 is of S-configuration.

Claim 17 (original): The salt of claim 12, wherein aa^1-aa^2 is (R)-Phe-(S)-Pro and the fragment $-NH-CH(R^1)-B(OH)_2$ is of R-configuration.

Claim 18 (original): The salt of claim 13 wherein the boronic acid is of formula (IX):

$X-(R)-Phe-(S)-Pro-(R)-Mpg-B(OH)_2(IX),$

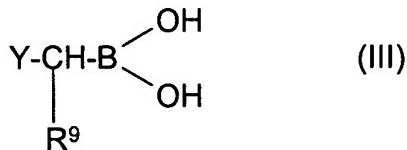
wherein X is $R^6-(CH_2)_p-C(O)-$, $R^6-(CH_2)_p-S(O)_2-$, $R^6-(CH_2)_p-NH-C(O)-$ or $R^6-(CH_2)_p-O-C(O)-$ wherein p is 0, 1, 2, 3, 4, 5 or 6 and R^6 is H or a 5 to 13-membered cyclic group which is unsubstituted or substituted by 1, 2 or 3 substituents selected from halogen; amino; nitro; hydroxy; a C_5-C_6 cyclic group; C_1-C_4 alkyl and C_1-C_4 alkyl containing, or linked to the cyclic group through, an in-chain O atom, the aforesaid alkyl groups optionally being substituted by a substituent selected from halogen, amino, nitro, hydroxy and a C_5-C_6 cyclic group.

Claim 19 (original): The salt of claim 12 which comprises a divalent metal salt of the peptide boronic acid.

Claim 20 (original): A pharmaceutical formulation adapted for oral administration which comprises a salt of claim 1.

Claim 21 (currently amended): A The salt of claim 1 wherein the organoboronic acid is of formula (III) below when included in a pharmaceutical formulation adapted for oral administration and comprising

- a) a first species selected from a boronic acid of formula (III), and said boronic acid when in the form of boronate ions of said boronic acid and thereof equilibrium forms of said boronic acid and said boronate ions, and combinations thereof:



wherein

Y comprises a moiety which, together with the aminoboronic acid residue -NHCH(R⁹)-B(OH)₂, has affinity for the substrate binding site of thrombin; and

R⁹ is a straight chain alkyl group interrupted by one or more ether linkages and in which the total number of oxygen and carbon atoms is 3, 4, 5 or 6 or R⁹ is -(CH₂)_m-W where m is from 2, 3, 4 or 5 and W is -OH or halogen; and

- (b) a second species selected from multivalent metal ions having a valency n,

wherein the formulation has an observed stoichiometry of first to second species essentially consistent with a notional stoichiometry of n:1.

Claim 22 (original): A method of inhibiting thrombin in the prophylaxis or therapy of disease, comprising parenterally administering to a mammal suffering from, or at risk of suffering from, thrombosis a therapeutically effective amount of the salt defined in claim 1.

Claim 23 (original): A method for preventing thrombosis in a haemodialysis circuit of a patient, for preventing a cardiovascular event in a patient with end stage renal disease, for preventing venous thromboembolic events in a patient receiving chemotherapy through an indwelling catheter, for preventing thromboembolic events in a patient undergoing a lower limb arterial reconstructive procedure, or for treating by way of therapy or prophylaxis an arterial disease selected from acute coronary syndromes, cerebrovascular thrombosis, peripheral arterial occlusion and arterial thrombosis resulting from atrial fibrillation, valvular heart disease, arterio-venous shunts, indwelling catheters or coronary stents, the method comprising parenterally administering to a mammal a therapeutically effective amount of the salt defined in claim 14.

Claim 24 (original): A medicament adapted for oral administration and comprising a therapeutically effective amount of a multivalent metal salt of a boronic acid which is a selective thrombin inhibitor and has a neutral aminoboronic acid residue capable of binding to the thrombin S1 subsite linked through a peptide linkage to a hydrophobic moiety capable of binding to the thrombin S2 and S3 subsites, the salt comprising a cation having a valency n and having an observed stoichiometry consistent with a notional stoichiometry (boronic acid:cation) of n:1.

Claim 25 (original): A medicament of claim 24 which is in solid dosage form.

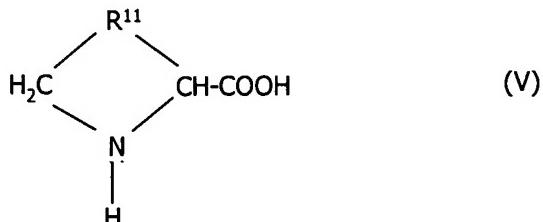
Claim 26 (original): A medicament of claim 25 wherein the boronic acid has a Ki for thrombin of about 100 nM or less.

Claim 27 (original): A method for making a salt of claim 12, comprising:
combining in a solvent diethanolamine and an ester of a boronic acid as defined in claim 12;
allowing or causing a precipitate to form and recovering the precipitate;
converting the precipitated material into the free organoboronic acid by contacting the precipitated material with an aqueous acid or base;
reacting the organoboronic acid with a base of a pharmaceutically acceptable multivalent metal to form to a salt as defined in claim 12;
the method further optionally comprising formulating the salt into an oral pharmaceutical formulation.

Claim 28 (new): The salt of claim 12, wherein:

aa¹ is selected from Phe, Dpa and wholly or partially hydrogenated analogues thereof;

aa² is a residue of an imino acid of formula (V);



where R¹¹ is -CH₂-, -CH₂-CH₂-, -S-CH₂-, -S-C(CH₃)₂- or -CH₂-CH₂-CH₂-, and,

when the formula (IV) ring is 5- or 6- membered, the formula (IV) ring is unsubstituted or is substituted at one or more -CH₂- groups by from 1 to 3 C₁-C₃ alkyl groups;

R⁹ is a straight chain alkyl group interrupted by one or more ether linkages and in which the total number of oxygen and carbon atoms is from 3 to 6.

Claim 29 (new): The salt of claim 28 wherein aa¹ is of (R)-configuration, aa² is of (S)-configuration, and chiral centre -NH-CH(R⁹)-B(OH)₂ is of (R)-configuration.

Claim 30 (new): The salt of claim 29 wherein R⁹ is alkoxyalkyl containing 4 carbon atoms, aa¹ is Phe or a wholly or partially hydrogenated analogue thereof, and aa² is azetidine-2-carboxylic acid or proline.

Claim 31 (new): The salt of claim 30 wherein R⁹ is 3-methoxypropyl.

Claim 32 (new): The salt of claim 29 wherein the multivalent metal is calcium, magnesium or zinc.

Claim 33 (new): The salt of claim 30 which is a hemicalcium, hemimagnesium or hemizinc salt.

Claim 34 (new): The salt of claim 31 which is a hemicalcium salt.

Claim 35 (new): The salt of claim 18 wherein X is R⁶-(CH₂)_p-O-C(O)-, where R⁶ is 5 to 13-membered aromatic or heteroaromatic group and p is 0 or 1.

Claim 36 (new): The salt of claim 1 wherein the boronic acid is of the formula:
Cbz-(R)-Phe-(S)-Pro-(R)-Mpg-B(OH)₂.

Claim 37 (new): The salt of claim 36 wherein the multivalent metal is calcium, magnesium or zinc.

Claim 38 (new): The salt of claim 36 which is a hemicalcium salt.

Claim 39 (new): The salt of claim 4 wherein R⁹ is 3-methoxypropyl and the carbon atom to which R⁹ is bonded comprises a chiral centre of (R)-configuration.

Claim 40 (new): The salt of claim 39 which is a hemicalcium, hemimagnesium or hemizinc salt.